Fungal infections of the lung are less common than bacterial and viral infections but pose significant problems in diagnosis and treatment. They mainly affect people living in certain geographic areas and those with immune deficiency. Their virulence varies from causing no symptoms to causing death.

Whom does it affect?

Epidemiology, prevalence, economic burden, vulnerable populations

Rates of invasive fungal infections have surged during recent decades, largely because of the increasing size of the population at risk. This population includes patients who are immunosuppressed because of diseases, such as cancers of immune cells of the blood, bone marrow, and lymph nodes, and those with human immunodeficiency virus (HIV) infection. It also includes patients taking immunosuppressive drugs, which are given to avoid rejection of transplanted organs or stem cells and as treatment for autoimmune diseases, such as rheumatoid arthritis. Immunosuppressive drugs are also given to reduce inflammation. For example, corticosteroids are often prescribed for many different lung diseases. A new class of potent immunosuppressive agents includes compounds that block regulatory molecules produced by the immune system called cytokines.
One of these cytokines, tumor necrosis factor, is key to many of the body’s immune processes. In addition, patients with chronic debilitating diseases, who are in an immune-deficient state, make an attractive host for invasive fungi.

Massive population growth, urban development, and climate change are also factors that have increased the prevalence of fungal infections in certain areas and are putting more people at risk of becoming infected with the fungi that is endemic to where they live. More recently, natural disasters such as tsunamis and hurricanes have also contributed to the changing epidemiology of fungal infections.

The financial and social burdens of fungal infections are staggering. Using National Hospital Discharge Data Sets from 1998, the annual cost of fungal infections...
infections in the United States was estimated to be $2.6 billion, approximately 0.24 percent of total U.S. healthcare expenditures (1). That same year, the average added expenditure to treat a patient with a fungal infection in the United States was more than $31,000 above the average annual healthcare expenditure of $4,000 per person (1). Most of this expense was incurred caring for hospitalized patients with invasive aspergillosis, a fungal infection predominantly affecting the lungs (2).

Generally speaking, invasive fungal infections (termed mycoses) can be divided into two broad categories: the opportunistic and the endemic mycoses. Opportunistic fungal infections involve ubiquitous fungi and occur predominantly in individuals whose immune systems are compromised. These infections do not follow any particular geographic distribution and are seen with increasing frequency worldwide. Invasive pulmonary aspergillosis and systemic candidiasis are the most prevalent opportunistic fungal infections. Mold infections that were once considered rare are now emerging as significant infectious complications.
of the severely immune compromised. The fungus aspergillus is the leading cause of infection-related death in stem cell transplant recipients (3). Allergic lung diseases can also develop in otherwise healthy subjects who are repeatedly exposed to environmental molds.

On the other hand, endemic fungal infections follow distinct geographic distributions that are determined by soil and climate conditions optimal for the fungi’s growth. North America is home to three of the major endemic mycoses: histoplasmosis, blastomycosis, and coccidioidomycosis. Their prevalence varies by region.

These three endemic fungal diseases share many characteristics. Illness is acquired by inhaling aerosolized spores. Healthy individuals who contract these diseases generally experience few symptoms, or, if they become ill, recover quickly on their own. In contrast, the infections can be life-threatening in patients with depressed immunity, especially those with acquired immune deficiency syndrome (AIDS) and those receiving immunosuppressive medications. The infections can persist and cause other lung diseases, such as emphysema, to worsen.

What are we learning about lung fungal infections?

Pathophysiology, causes: genetic, environment, microbes

Most pulmonary fungal infections occur after inhalation of fungi that have been aerosolized because their natural habitat was disturbed. Once in the lungs’ alveoli (air sacs), the fungus is engulfed by macrophages and other cells involved in the primary immune response. Macrophages are usually able to neutralize and destroy the pathogens that they attack, but many fungi have developed a way to disable the macrophage’s weapons, and some fungi have actually developed the ability to grow and multiply inside macrophages.

Secondary or adaptive immunity cells are called to the site of infection, and in healthy individuals, this action can usually control the infection’s spread. The fungus is contained, but the sites of initial infection can remain as granulomas, collections of different types of immune cells. The granulomas later degenerate to scars and often calcify. Calcified granulomas may be seen years later on x-ray images.

When cellular immunity is impaired, as it is, for instance, in AIDS, infection with an endemic fungus cannot be controlled. Almost any organ can be involved
as the infection spreads throughout the body. The presence of structural lung disease, such as emphysema, impairs the clearance of the infection and allows a chronic condition to take hold. White blood cells (especially neutrophils) are critical to fight certain fungal infections such as those due to the fungus *Aspergillus*.

CASE STUDY

A 66-year-old Indiana woman was hospitalized for an abnormal chest radiograph and respiratory symptoms. Five years earlier, she had been diagnosed with sarcoidosis and treated with an immunosuppressive drug, azathioprine. Three months earlier, infliximab, a new potent anti-cytokine (tumor necrosis factor) immunosuppressive agent, had been started. One month before hospital admission, she developed fever, weakness, shortness of breath, productive cough, nausea, and vomiting, leading to dehydration and a 20-pound weight loss. A chest computed tomography scan showed small nodules scattered in both lungs. She continued to worsen despite many courses of antibacterial antibiotics. In the hospital, her blood pressure dropped. She had fever and a rapid heart rate. Her oxygen level fell and she needed supplemental oxygen. Bronchoscopy with transbronchial biopsy showed granulomas containing the fungus *Histoplasma*. Urine *Histoplasma* antigen was positive. She was treated with a potent but potentially toxic antifungal agent, amphotericin B. She improved and was discharged to a long-term care facility after a prolonged hospitalization that was complicated by respiratory failure requiring mechanical ventilation.

Comment

Infection by the fungus *Histoplasma capsulatum*, or histoplasmosis, is one of the most common infectious complications of medicines that block the inflammatory mediator tumor necrosis factor. Delay in establishing the diagnosis and initiating the appropriate antifungal therapy usually occurs because fungal infections are much less common and harder to diagnose than bacterial pneumonia, which they resemble. Furthermore, the risk of invasive fungal infections in patients receiving anti-cytokine therapy is under-recognized despite the much wider use of these agents today. Delayed diagnosis and treatment can lead to a tragic outcome.
A number of recent studies suggest that climate changes have disrupted the natural habitat of some endemic fungi, leading to significant changes in their epidemiology. One revealing example is the noticeable increase in the incidence of the fungus coccidioidomycosis, which has been linked to distinct patterns of environmental and climatic change in parts of Arizona between 1998 and 2001. Other examples include the expanding geographic distribution of blastomycosis in the mountains of Northeast Tennessee and the recent outbreak of Cryptococcus gattii, a fungus previously associated with tropical and subtropical climates, in the Pacific Northwest.

How are fungal infections prevented, treated, and managed?

**Prevention, treatment, staying healthy, prognosis**

Despite years of research and much progress in the field, no fungal vaccine is available for clinical use. Today, the most effective way of preventing fungal infections in individuals at risk is by avoiding activities that are associated with
exposure to the fungi. Antifungal medication to prevent infection is recommended only in patients with severe immunosuppression, especially since it may lead to the emergence of fungi that are resistant to these medications.

During the last two decades, the number of antifungal agents available for clinical use has increased. Until the mid-1980s, amphotericin B had been the antifungal drug of choice for most fungal infections. At least a half dozen new drugs, which are less toxic than amphotericin B, are now used to treat fungal infections. Amphotericin B is still used in the initial treatment of severe and central nervous system fungal infections. It is usually followed by a maintenance regimen using the new medications.

Immunosuppressed patients should be educated about their risk for developing fungal infections and advised about activities they should avoid, symptoms of fungal disease, and when to report possible exposure or symptoms to their doctor. High-risk activities include demolition and renovation of old buildings, clearing shrubs and debris, and spelunking.

For the most part, treatment of endemic pulmonary fungal infections is very effective, especially when patients are diagnosed and treated in a timely fashion. For the opportunistic fungal infections, the prognosis depends mostly on the immune state of the patient. Therapy is more likely to be effective if immunity is recovered. The most striking example is the impact of anti-retroviral therapy for HIV, which has greatly reduced the incidence and outcome of opportunistic fungal infections in patients infected with HIV.

Are we making a difference?

Research past, present, and future

During the past two decades, research has led to significant advancements in the diagnosis and treatment of fungal infections. Previously, diagnosis was possible only by isolating the organism. Today, urinary and blood tests are used in clinical practice for the rapid diagnosis of invasive fungal infection.

Drug discovery and development have resulted in reformulation of old drugs with a great reduction in toxicity, expansion of individual classes of drugs with better coverage of more fungi, and new classes of drugs with increased efficacy and fewer side effects.

It is now recognized that many fungi that were once routinely dismissed as contaminants are true human pathogens, although mostly for severely immune
compromised patients. These include the zygomycetes and a variety of molds. Even more worrisome is that several of these organisms are resistant to standard treatment and there is no sensitive diagnostic test. In addition, resistant species of common fungi such as Candida and Aspergillus are also on the rise.

**What we need to cure or eliminate fungal lung disease**

Because fungi are everywhere in soil (about 75,000 species have been identified), it is not possible to consider eliminating fungal infections. Although great progress has been made in diagnosing and treating the illnesses they cause, improvement is still needed in all areas. As science gains a better understanding of their basic mechanisms of action, new targets to interrupt the life cycle of the fungi or to strengthen the host immune system are being identified.

The most important immediate step in controlling fungal infections is to increase awareness among clinicians of the significance of these pathogens and the changing patient population at risk. Longer term, it is essential that new diagnostic tests be developed that can provide a rapid and accurate diagnosis, especially for the emerging pathogens. It also will be important to be able to predict their susceptibility to drugs. Researchers must continue to search for novel agents that target key molecular pathways to combat organisms that are resistant to current antifungal therapy. Alterations in the host immune response to fungi could boost clearance of the infection and limit the damage to lung tissue.

Research must also continue to address the interface of the host and fungal pathogen. Knowing how the human host recognizes and counteracts invading fungi and how fungi evade the immune system and survive inside the host cells is important for controlling and eliminating infection. Researchers have identified a number of fungal factors necessary to establish the disease—knowledge of which may eventually lead to a vaccine.
REFERENCES


WEB SITES OF INTEREST

Medline Plus  

Centers for Disease Control and Prevention  
Division of Bacterial and Mycotic Diseases, Mycotic Diseases Branch  
[www.cdc.gov/ncidod/dbmd/mbd/goals.htm](http://www.cdc.gov/ncidod/dbmd/mbd/goals.htm)

Infectious Disease Society of America  
[www.idsociety.org](http://www.idsociety.org)